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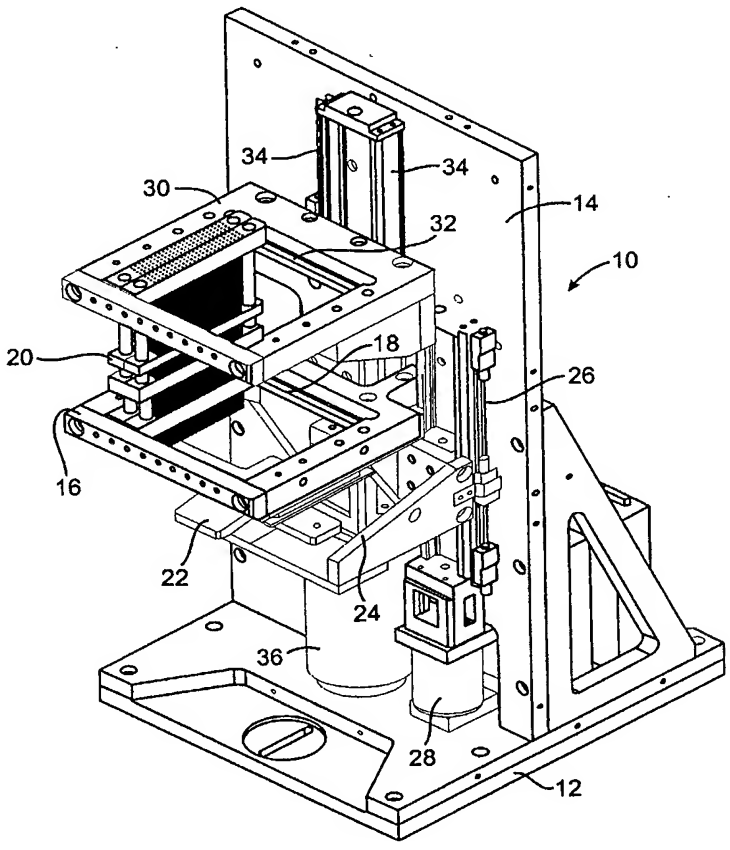
(54) Title: SYRINGE ARRAY SYSTEM AND METHOD

(57) Abstract

The invention provides systems and methods for dispensing liquids. One liquid dispenser comprises a base member (12) and at least 864 syringes that are operably coupled to the base member (12). Each syringe has a distal tip, and the syringes are each configured to aspirate and dispense a substantially equal volume of liquid. Further, the syringe tips are disposed within an area that is less than about 80 cm^2.



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SYRINGE ARRAY SYSTEM AND METHOD

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part application of copending U.S. Patent Application Serial No. 09/260,368, filed March 1, 1999, the complete disclosure of which is herein incorporated by reference.

BACKGROUND OF THE INVENTION

The invention relates generally to the field of liquid dispensing, and in particular to the dispensing of liquids into relatively small wells. More specifically, the invention provides for the dispensing of precise volumes of liquid into plates having a high density of wells.

In various fields of chemical and biological research, there is a need to place known volumes of liquids within wells to facilitate the performance of various procedures. One common procedure is the performance of assays where various chemicals or substances are introduced into the wells and any reactions are evaluated. As another example, synthesized chemical compounds which have been cleaved from solid supports are typically transferred to sample wells for analysis. Various liquids are introduced into the wells to assist in identifying a particular compound as generally known in the art.

The wells which receive the liquids are often formed in plates having a standard arrangement or format. For example, one common format is a 96 well format where the plate is generally rectangular in geometry and has its wells arranged in eight rows and twelve columns. The outer dimensions of such plates are typically about 8.53 cm by about 12.78 cm. Typically, the wells are disposed within a rectangular area of about 80 cm^2. Another common well format is a 384 well format which has 384 wells in the same area utilized by 96 well formats. As such, the 384 well format has a higher density of wells.

Such multi-well plates are well known within the art and are available from a host of commercial suppliers, such as Polyfiltronics. The use of standard sized plates is advantageous because such plates may be used with most commercially available handling and processing equipment. For example, most automated plate readers, some

speed vacuum concentrators, autosamplers, robotics liquid handling equipment, and the like, are configured to operate with standard 96 and 384 multi-well plate formats.

Of particular interest to the invention are automated dispensing systems which are employed to dispense fluids into the wells of such plates. A wide variety of automated dispensing equipment exists for both 96 and 384 well formats, including the Platemate 96/384 Automated Pipettor, from Matrix Technologies Corporation; The Multi-Spense 384/96 Wells Micro-Plate Filler, from V&P Scientific, Inc.; the Multidrop dispenser, from Tirerrek; the Hydra 96, from Robbins Scientific; The Q Fill2, from Genetix Limited; the Embla 384, from Skatron Instruments; the Genesis Logistics Workstation, from Tecan; and the Finnpipette 384, from Labsystems.

Another type of format that is becoming increasingly useful is an 864 well format having 24 rows and 36 columns of wells which are disposed in the same area utilized by 96 well plates. The use of 864 well formats is becoming more popular as the need to evaluate larger chemical libraries in a more efficient manner increases. Reduction in the size of the wells is also advantageous because less chemicals (which can often be relatively expensive) are needed.

The 864 well format has outer dimensions similar to 96 and 384 well formats to take advantage of existing automated equipment. However, due to the relatively small size and close spacing of the wells in an 864 well plate, such a format cannot efficiently be used with existing automated filling equipment. Indeed, at present no 864 channel dispensing systems are known to be available.

Hence, it would be desirable to provide improved apparatus, systems, and methods for transferring liquids into wells of multi-well plates, especially those plates having at least 864 wells. In particular, it would be desirable to provide ways to rapidly and efficiently fill such wells with the desired liquids. Still further, the systems and methods should allow for precise volumes of liquids to be transferred into the wells.

SUMMARY OF THE INVENTION

The invention provides exemplary liquid dispensing systems and methods, along with exemplary syringe assemblies and syringe assembly units. In one exemplary embodiment, a liquid dispenser is provided which comprises a base member and at least 864 syringes which are operably coupled to the base member. The syringes are each configured to aspirate and dispense a substantially equal volume of liquid. Further, each syringe has a distal tip, with the syringe tips being disposed within an area that is less than

about 80 cm^2. In this way, 864 or more syringes may be used to transfer liquids to wells of multi-well plates having at least 864 wells which are disposed within an area similar to most 96 and 384 multi-well plates. Hence, one advantage of the invention is that the liquid dispenser has a high density of syringes so that all 864 wells of an 864 well plate may simultaneously be filled with a metered volume of liquid.

Preferably, each syringe is configured to aspirate and dispense liquids having a volume in the range from about 10 nl to about 10 µl. Also, an actuation assembly is preferably provided to actuate aspiration and dispensing of the liquid.

In one particular aspect, a hydrophobic coating is disposed on a distal tip and an outside surface of each syringe. For example, the hydrophobic coating may comprise a silicone based coating. Such a coating is particularly useful when dispensing volumes that are less than about 1 µl into a dry well. The hydrophobic coating ensures that the liquid is dispensed in droplet form, without adhering to the distal tip or the outer surface of the syringe. In this way, the droplet may be contacted with a bottom end of a well to transfer the liquid into the well when the syringe tip is moved away from the bottom end of the well.

In another exemplary embodiment, the invention provides a liquid dispensing system which comprises a base member, and a movable mount movably coupled to the base member. A plurality of syringe units are removably mounted to the mount, and each syringe unit includes an array of syringes. Further, the syringes are each configured to aspirate and dispense a liquid upon movement of the mount.

In one aspect, a tray is provided which is configured to receive a multi-well plate. The tray may be configured to move the multi-well plate such that the syringes are placed into the wells of the plate. Alternatively, a robot may be employed to deliver and position a multi-well plate relative to the syringes.

In one particular aspect, each syringe unit or module includes a 24 by 4 array of syringes, and the moveable mount is configured to hold nine syringe units. In this way, 864 syringes are provided so that all 864 wells of an 864 well plate may simultaneously receive a liquid.

In another aspect, each syringe includes a syringe body and a plunger which is movable within the syringe body to aspirate liquids into the syringe body and to dispense liquids from the syringe body. Preferably, each plunger is operably coupled to the moveable mount such that movement of the moveable mount moves the plungers within the syringe bodies. In one preferable aspect, a proximal portion of each syringe

body is collapsible when the mount is moved to move the plungers. As one example, the proximal collapsible portion may comprise a tubular outer guide which slides over a tubular inner guide when the mount is moved. A fixed mount is preferably also provided to hold a distal portion of the syringe bodies.

The invention further provides an exemplary syringe assembly which comprises at least one tubular plunger guide and a needle coupled to the plunger guide. The needle includes a lumen which terminates at an open distal tip. The assembly further includes a plunger that is moveable within the plunger guide and the needle. A sealing mechanism is disposed to form a seal between the needle and the plunger guide and between the plunger and the seal member. In this way, liquids may be aspirated into the lumen of the needle when the plunger is retracted, and liquids may be dispensed from the lumen of the needle when the plunger is extended.

The syringe assembly preferably includes a pair of tubular plunger guides, with one of the guides being an inner guide and the other being an outer guide. The inner guide is disposed within the outer guide, and the plunger guides slide relative to each other during movement of the plunger. Optionally, a guide plate may be disposed to maintain the inner and outer plunger guides in axial alignment.

The syringe assembly may also include a center plate and a lower plate which are fixed relative to each other. With this configuration, the needle is held by the lower plate, and the inner guide is held by the middle plate. A top plate is preferably also provided, and both the outer guide and the plunger are preferably coupled to the top plate. Further, the top plate is moveable relative to the middle plate to move the plunger within the needle.

In another aspect, a stop is provided to limit the movement of the top plate relative to the center plate. In this way, the amount of travel of the plunger may be controlled. In still another aspect, the sealing mechanism comprises a tubular seal member disposed between the inner plunger guide and the needle. The sealing mechanism further includes a protrusion that is coupled to the inner guide, and a biasing member that is disposed between the center plate and the protrusion to force the inner plunger guide against the seal member.

In still yet another aspect, the needle has a distal portion with an outer diameter that is less than about 0.7 mm when used to dispense volumes of about 5 μl, and less than about 0.8 mm when used to dispense volumes of about 10 μl. In one particularly preferable aspect, the needle is capable of dispensing liquids having a volume

in the range from about 10 nl to about 10 µl. In still another aspect, the distal tip and the outer surface of the needle may be provided with a hydrophobic coating.

In another embodiment, the invention provides an exemplary syringe assembly unit having a plurality of syringe assemblies which are constructed similar to those just described. The syringe assembly unit further comprises a holding system to hold the syringe assemblies. In one aspect, the holding system comprises a sliding mount and a fixed mount. In this way, the plungers may be moved within the needles by moving the sliding mount relative to the fixed mount. One advantage of utilizing the holding system is that multiple syringe assembly units may be held within the sliding mount so that a relatively large number of needles may be provided within a relatively small space. For example, the needle tips may be spaced apart by a distance as small as about 1 mm. In this way, liquids may be dispensed into wells of a plate having a relatively large density of wells. In one aspect, the sliding mount is slidably coupled to a track, and a motor is provided to move the slidable amount along the track. In this way, all of the syringe assemblies which are coupled to the mount may have a liquid dispensed simply by operating the motor to move the mount.

The invention further provides an exemplary method for dispensing liquids. According to the method, a plate is provided having at least 864 wells. Further, the wells are disposed in an area that is less than about 80 cm^2. A liquid is aspirated into at least 864 syringes, and a substantially equal volume of liquid is dispensed from each of the syringes and into the wells of the plate.

In one particular aspect, a liquid having a volume in the range from about 10 nl to about 10 µl is dispensed from each syringe. In another aspect, each syringe has a syringe body and a plunger that is disposed within the syringe body. The liquid is aspirated by retracting the plunger within a distal portion of the syringe body, and the liquid is dispensed by extending the plunger within the distal portion. Preferably, a proximal portion of the syringe body is compressed to extend the plunger within the distal portion. Such a configuration is particularly advantageous in that the syringe bodies have zero dead volume so that all of the liquid aspirated may be dispensed. In this way, essentially none of the transferred liquid is wasted.

In yet another aspect, movement of each plunger is initiated at substantially the same time, and each plunger is moved at substantially the same rate. In this way, a substantially equal volume of liquid is dispensed at substantially the same time from each syringe. Preferably, the liquid is dispensed with a precision that is less

than about 6% CV at about 0.1 µl per well. According to the method, the amount of liquid dispensed may be incremented in increments in the range from about 10 nl to about 10 µl.

In still another aspect, the liquid to be transferred may be formed as a droplet by providing a hydrophobic coating on a distal tip and an outside surface of the syringe. The syringes are moved in close proximity to a bottom end of the wells to permit the droplets to contact the bottom ends of the wells. The syringes are then raised to transfer the droplets into the wells. Such a process is particularly useful when dispensing small volumes into dry wells.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view of an exemplary liquid dispensing system according to the invention.

Figs. 1A, 1B and 1C are side, top and front views, respectively, of the system of Fig. 1.

Fig. 2 is a side view of a syringe assembly unit of the system of Fig. 1 which includes a plurality of syringe assemblies.

Fig. 3 is an end view of the unit of Fig. 2.

Fig. 4 is a top view of the unit of Fig. 2.

Fig. 5 is a side view of a plunger from one of the syringe assemblies of Fig. 2.

Fig. 6 is a side view of an outer plunger guide from one of the syringe assemblies of Fig. 2.

Fig. 7 is a side view of an inner guide assembly from one of the syringe assemblies of Fig. 2.

Fig. 8 is a side view of a needle from one of the syringe assemblies of Fig. 2.

Fig. 9 is a cross sectional side view of a top portion of the unit of Fig. 2.

Fig. 10 is a cross sectional side view of a middle portion of the unit of Fig. 2.

Fig. 11 illustrates the system of Fig. 1 with dispensing needles being inserted into the wells of a multi-well plate, and with a moveable mount being raised to retract plungers within the needles.

Fig. 12 illustrates the system of Fig. 11 with the moveable mount being lowered to extend the plungers within the needles to dispense a liquid into the wells.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The invention provides exemplary systems, assemblies and methods to aspirate and dispense liquids in relatively small volumes. To aspirate and dispense the liquids, the invention utilizes syringes which are relatively small in size and are spaced close together so that they can be used with multi-well plates having a high density of wells. Preferably, all of the syringes are configured so that they may be actuated at substantially the same time. In this way, each syringe is able to aspirate and dispense at substantially the same time with substantially the same volume. In this manner, plates having a relatively high density of wells may simultaneously have all of its wells simultaneously filled with a metered volume of liquid.

The invention will find its greatest use with multi-well plates having 864 wells that are disposed within an area of about 80 cm^2. As such, the 864 well plates may be constructed to have an outer perimeter which is compatible with existing automated processing and handling equipment. Although the invention will find its greatest use with 864 well plates, it will be appreciated that the invention is useful with other plates having different numbers of wells. For example, in some cases the invention may be utilized with standard plates having less than 864 wells, e.g., 96 and 384 well plates, as well as those having more than 864 wells, e.g., 1536 well plates. Moreover, it will be appreciated that the invention may be utilized with multiwell plates which do not have the same footprint utilized with existing 96 and 384 well plates. As such, the invention may be modified to include essentially any number of syringes in a wide variety of arrangements so that it may be compatible with plates having essentially any number and/or arrangement of wells.

The 864 well plates utilized with the invention preferably have wells that define a volume in the range from about 2 µl to about 20 µl. The use of such relatively small volumes is advantageous in that a minimal volume of liquid may be placed into each of the wells. This is particularly advantageous with processes where the liquid is relatively expensive. By minimizing the amount of liquid aspirated and dispensed, the expense of the process may be reduced. Also, the use of such relatively small volumes allows for a relatively high density of wells within a given area. In this manner, the

throughput of the system may be greatly increased since significantly more wells may be utilized within the same area.

The syringes of the invention are preferably configured so that they are able to dispense volumes in the range from about 10 nl to about 10 µl, and more preferably in the range from about 100 nl to about 10 µl. This range of volumes may be dispensed into wells that already include fluid, or into dry wells. When dispensing small volumes into wells already having a liquid, the liquid forced out of the syringes may be contacted with the liquid to facilitate its transfer from the syringe. To dispense volumes that are less than about 1 µl into a dry well, the syringes may be provided with a hydrophobic coating on their distal tips and outside surfaces. One example of such a coating is a silicone based coating. In this way, when the liquid is forced out of the syringe, the liquid is prevented from contacting the distal tip and the outer surface, thereby forming a droplet. This droplet may then be contacted against a dry bottom end of a well to transfer the droplet into the well.

The syringes are preferably configured so that they are able to deliver such volumes in increments as low as 10 nl and more preferably in the range from about 50 nl to about 2 µl. Another advantage of the syringes of the invention is that they are able to deliver precise volumes of liquid, preferably less than about 6% CV for fill volumes in the range from about 100 nl to about 10 µl, it being appreciated that substantially lower CV percentages are obtainable within the higher fill volume ranges.

In one aspect of the invention, the syringes are preferably in arranged in units or modules. Typically, each unit includes a two dimensional array of syringes. Multiple units may then be combined together to form a system of syringes. Hence, the number of syringes in the system may be varied simply by varying the number of syringes in the units and/or by varying the number of units. Merely by way of example, for an 864 syringe system, each unit may include a 24 by 4 array of syringes, with the system including 9 syringe units. However, it will be appreciated that other arrangements may be utilized.

The syringes of the invention preferably utilize a plunger which moves through a needle to displace a volume of liquid that is substantially equal to the volume displaced by the plunger. Similarly, the syringes aspirate liquids by retracting the plunger to create a vacuum within each needle. With such a construction, the syringes have zero dead volume so that all of the liquid that is aspirated is dispensed. Further, the volume

aspirated and dispensed may be varied by varying the length of the stroke of the plunger and/or by varying the size of the plunger.

The plunger-in-needle design of the invention is also useful in reducing the amount of space between the needles to increase the density of the needles. In this way, liquids may efficiently be dispensed into plates having a high density of wells. For example, the needles of the invention may be spaced apart by a distance as small as 1 mm. For dispensing into 864 well plates, the distance between the needles is preferably about 3 mm.

The invention also utilizes a holding system which holds the syringes such that the needle tips remain precisely laterally spaced apart and remain positioned within the same plane during aspiration and dispensing. In this way, the needle tips may repeatedly be positioned within all wells of a multi-well plate at a proper and consistent depth. Preferably, the variability in the position of the needle tips within a given plane is less than about 0.1 mm. When dispensing, the plungers are preferably moved while the position of the needle tips remains fixed to ensure accurate dispensing.

The syringe or needle tips are preferably placed into the wells of a multi-well plate by moving the syringe tips into the wells, by moving the multi-well plates relative to the syringe tips, or both. In one particularly preferable embodiment, a robot is utilized to grasp and deliver the multi-well plate to the dispensing system. The arm of the robot is also used to position the plate such that the syringe tips are disposed within the wells. For example, one type of robot that may be utilized is an ESC-200 robot, commercially available from Equip Technologies.

Referring now to Figs. 1 and 1A-1C, an exemplary system 10 for aspirating and dispensing liquids will be described. System 10 is constructed of a base member 12 having a back plate 14. Securely coupled to back plate 14 is a fixed mount 16. Fixed mount 16 includes a lip 18 onto which multiple syringe assembly units 20 are held. For convenience of illustration, only two of a possible 9 units are shown. As described in greater details hereinafter, each syringe assembly unit 20 includes a plurality of syringes having needles whose distal tips extend below fixed mount 16. In this way, the needle tips may be introduced into the wells of a multi-well plate by placing the multi-well plate beneath fixed mount 16 and raising the multi-well plate until the needle tips are within the wells.

Conveniently, system 10 further includes a movable tray 22. Tray 22 is movable in a vertical direction so that when a multi-well plate is positioned on tray 22,

the multi-well plate may be lifted to have the needle tips placed within its wells. Tray 22 is coupled to an arm 24 which in turn is slidably coupled to a track system 26 which is coupled to back plate 14. A servo motor 28, having a lead screw (not shown) is employed to slide arm 24 vertically up and down along track system 26. In this way, motor 28 may be employed to vertically raise and lower tray 22 so that the multi-well plate may be properly positioned with respect to the needle tips of the syringes within units 20. Alternatively, a separate robot (not shown) may be utilized to properly position the wells of a multi-well plate with respect to the syringes. In this way, tray 22 would not be needed.

System 10 also includes a sliding mount 30 which is configured to move vertically up and down with respect to fixed mount 16. Sliding mount 30 includes a lip 32 into which syringe assembly units 20 are also coupled. Preferably, units 20 are coupled to fixed mount 16 and to sliding mount 30 by use of clamps (not shown). However, it will be appreciated that a variety of fastening mechanisms may be used including screws or other fasteners which are placed through fixed mount 16 and sliding mount 30, welds, and the like.

As described in greater detail hereinafter, sliding mount 30 is lowered to dispense liquids from each of the syringes. Conversely, sliding mount 30 is raised relative to fixed mount 16 to create a vacuum within the syringes so that liquid may be aspirated into the syringes. Although not shown, a protective cover plate is preferably disposed on top of sliding mount 30 after each of the syringe assembly units 20 has been inserted.

Sliding mount 30 is slidably coupled to a track system 34 which is coupled to back plate 14. A servo motor 36 with a lead screw (not shown) is employed to vertically raise and lower sliding mount 30 along track system 34. Exemplary motors which may be utilized for both motor 36 and motor 28 are AVS servo motors, commercially available from Bearing Engineers, Inc.

Although not shown, a control system may be coupled to motors 28 and 36 to control the amount of movement of tray 22 as well as sliding mount 30. As described in greater detail hereinafter, by controlling the amount of vertical movement of sliding mount 30, the volume of liquid aspirated or dispensed from the syringes may be precisely controlled. An exemplary control system which may be utilized includes a Pentium-based personal computer which includes interface software and which is coupled to a controller. In turn, the controller is configured to send high voltage signals to an

amplifier or driver which converts the voltage signal to current which drives the motors. An exemplary controller which may be utilized is a DMC-1040 unit, commercially available from Galil. An exemplary driver which may be utilized is an AVS driver, commercially available from Bearing Engineering, Inc.

Referring now to Figs. 2-4, construction of one of the syringe assembly units 20 will be described in greater detail. First, the outer framework of unit 20 will be described. Second, a detailed discussion of the manner of construction of each syringe will be described.

Unit 20 is framed by utilizing a lower plate 38 and a center plate 40. Both lower plate 38 and center plate 40 include a two dimensional array of through holes 42 and 44, respectively, through which syringe assemblies 46 are disposed. As shown, unit 20 includes a 24 by 4 array of syringe assemblies 46. As such, through holes 42 and 44 are 96 in number. Positioned between lower plate 38 and center plate 40 are a pair of support posts 48. Screws 50 are employed to securely connect post 48 to both lower plate 38 and center plate 40. In this way, the position of lower plate 38 is fixed relative to center plate 40. As best shown in Fig. 1, lower plate 38 is coupled to fixed mount 16 so that both the position of lower plate 38 and center plate 40 are fixed relative to mount 16 (as well as to back plate 14).

Lower plate 38 and center plate 40 are preferably constructed of a rigid material, such as aluminum. Through holes 42 and 44 are fashioned to have a size sufficient to allow the relevant portions of syringe assemblies 46 to slide through the through holes as described in greater detail hereinafter.

Also framing syringe assembly unit 20 is a top plate 52. Coupled to top plate 52 by screws 54 are a pair of plunger stops 56. As shown, plunger stops 56 are resting upon center plate 40. As such, downward movement of top plate 52 relative to center plate 40 is prevented. Top plate 52 may be vertically raised relative to center plate 40 simply by lifting top plate 52.

As best shown in Fig. 1, top plate 52 is secured to sliding mount 30. In this way, as sliding mount 30 is vertically raised and lowered, top plate 52 is vertically raised and lowered with respect to both center plate 40 and lower plate 38. When plunger stops 56 engage center plate 40, further downward movement of sliding mount 30 is prevented.

As described in greater detail hereinafter, a top portion of each of syringe assemblies 46 extends into top plate 52. As such, top plate 52 includes a plurality of

through holes 58 for receiving the syringe assemblies 46. Top plate 52 may be constructed of materials similar to those used for center plate 40 and lower plate 38.

Secured to plunger stops 56 by screws 60 is a guide plate 62. Guide plate 62 includes a plurality of through holes 64 which are sized such that the relevant portion of each syringe assembly 46 may slide through the through holes as described in greater detail hereinafter. Guide plate 62 serves as a lateral support for syringe assemblies 46 when top plate 52 is raised and lowered.

Referring also now to Figs. 5-9, construction of syringe assemblies 46 will be described in greater detail. Each syringe assembly 46 is constructed of a plunger 66 (see Fig. 5), an outer plunger guide 68 (see Fig. 6), an inner plunger guide assembly 70 (see Fig. 7), and a needle 72 (see Fig. 8). As best shown in Figs. 2, 5 and 9, plunger 66 has a proximal end 74 which is secured to a set screw 76 (see Fig. 9). The through holes 58 in top plate 52 include a threaded portion 78 into which set screw 76 may be screwed. In this way, plunger 66 may be securely coupled to top plate 52. Use of set screw 76 is advantageous in that the position of plunger 66 within needle 72 may be varied simply turning set screw 76. For example, in some cases, it may be desirable to have plunger 66 extend beyond needle 72 when dispensing to ensure the liquid is fully dispensed. The extent of travel of the distal end of plunger 66 may be variety simply by turning screw 72. The use of screw 72 is further advantageous in that it allows for easy installation and replacement of needle 66. For instance, if the needle needs to be replaced, screw 72 is simply removed and another needle and screw are inserted.

Resting a bottom portion of each through hole 58 is outer plunger guide 68 as best shown in Fig. 9. Plunger guide 68 has a flared end which rests upon a lip at the bottom of through hole 58. In this way, the position of outer plunger guide 68 relative to top plate 52 is fixed.

Outer plunger guide 68 is preferably constructed of a generally rigid material, such as stainless steel. Outer plunger guide 68 preferably has an outer diameter of about 1.3 mm, and an inner diameter of about 0.8 mm. As shown in Fig. 9, plunger 66 extends through outer plunger guide 68. Plunger 66 is preferably constructed of stainless steel, and has an outer diameter of about 0.36 mm.

As best shown in Figs. 2, 7 and 10, inner plunger guide assembly 70 comprises an inner plunger guide 80 over which an outer tube 82 is disposed. Disposed over outer tube 82 is a projecting member 84. Inner plunger guide 80 is preferably constructed of stainless steel and has an outer diameter of about 0.64 mm and an inner

diameter of about 0.365 mm. In this way, plunger 66 is able to slide within inner plunger guide 80. Outer tube 82 is preferably constructed of stainless steel and is bonded to inner plunger guide 80. Outer tube 82 preferably has an outer diameter of about 1.07 mm and an inner diameter of about 0.65 mm. The outer diameter of tube 82 is such that it may slide within through hole 42 of center plate 40. Projecting member 84 is preferably tubular in geometry and is preferably bonded to outer tube 82. Projecting member 84 is preferably constructed of stainless steel, and has an outer diameter of about 1.6 mm and an inner diameter of about 1.1 mm. As best shown in Fig. 10, projecting member 84 is employed to contain a spring 86 between projecting member 84 and center plate 40. As described in greater detail hereinafter, spring 86 assists in producing a seal so that plunger 66 is able to efficiently aspirate and dispense liquids.

Referring now to Figs. 2, 8 and 10, construction of needle 72 will be described in greater detail. Needle 72 includes a proximal portion 88, and central portion 90 and a distal portion 92 which terminates at a tip 94. Needle 72 is preferably constructed of stainless steel, and has an outer diameter of about 0.64 mm. Securely disposed over central portion 90 are a pair of tubes 90a and 90b. Tube 90a has an outer diameter which is larger than the diameter of through hole 44 so that it will rest on top of lower plate 38. Tube 90b has a diameter which allows it to fit within through hole 44 as best shown in Fig. 2.

A central lumen 96 extends through needle 72. Lumen 96 preferably has a diameter of about 0.365 mm. As best shown in Fig. 10, plunger 66 passes through lumen 96 and substantially fills lumen 96. In this way, plunger 66 is able to force substantially all of the liquid out of lumen 96 when translated through the lumen. In this manner, needle 72 has zero dead volume so that essentially all liquid aspirated is also dispensed.

Optionally, needle 72 may include a hydrophobic coating on its outside surface and at tip 94. Such a coating is used to ensure that the liquid being dispensed will not adhere to tip 94 or the outside surface. In this way, the liquid will form a droplet as plunger 66 is translated through lumen 96.

Proximal portion 88 is slidable within outer tube 82 as best shown in Fig. 10. Disposed between proximal portion 88 and inner plunger guide 80 is a tubular seal member 98 as best shown in Fig. 10. Seal member 98 is preferably constructed of PTFE and has an outer diameter of about 0.63 mm and an inner diameter of about 0.36 mm. The inner diameter of seal member 98 is selected so that a seal is produced about plunger 66, while still allowing plunger 66 to translate through seal member 98.

When assembled, bottom plate 38 forces proximal portion 88 against seal member 98. Also, spring 86 provides a compressive force, i.e. a preload, to compress seal member 98 between inner plunger guide 80 and proximal portion 88. In this way, a seal is also provided between needle 72 and inner plunger guide assembly 70. In this manner, liquids as well as gasses are prevented from leaking beyond seal member 98. Such a configuration is particularly advantageous when withdrawing plunger 66 from needle 72 to create a vacuum within needle 72 so that liquids may be aspirated into needle 72. Further, the preload provided by spring 86 allows seal member 98 to experience wear while still providing an effective seal between seal member 98 and plunger 66. In this way, maintenance of the unit is reduced. Use of spring 86 is further advantageous in that it allows the inner plunger guide 80 to be spring loaded, rather than needle 72. In this way, the position of the distal tip of needle 72 may be fixed during dispensing to allow the needle tip to be more accurately positioned during dispensing.

Also when assembled, lower plate 38 presses upward on tubes 90a which fixes the position of needle tips 94 relative to lower plate 38. In this way, the distance of each tip 94 from lower plate 38 may be precisely controlled so that the needle tips 94 lie within the same plane. Also, the lateral spacing between tips 94 may be precisely controlled so that tips 94 may accurately be positioned within wells of a multiwell plate. Since tips 94 do not move during dispensing, the accuracy of the system when dispensing is greatly improved.

Hence, syringe assembly units 20 operate by lifting top plate 52 relative to center plate 40 to withdraw plunger 66 from lumen 96 of needles 72. As top plate 52 is raised, outer plunger guide 68 slides over inner plunger guide 80 so that plungers 66 remain protected by and supported by a guide. Guide plate 62 also assists in maintaining plunger 66 axially straight when top plate 52 is raised and lowered.

As previously mentioned, when plunger 66 is retracted from lumen 96, a vacuum is created within lumen 96 so that liquid may be drawn into lumen 96. To dispense the liquid within needle 72, top plate 52 is lowered relative to center plate 40. In so doing, plunger 66 forces the liquid from lumen 96. As such, the amount of movement of top plate 52 may be controlled to control the amount of liquid that is dispensed. As top plate 52 is lowered, outer plunger guide 68 slides over inner plunger guide 80 so that the plunger guides will not interfere with movement of the top plate 52. When the distal tip of plungers 66 reaches tips 94 of needle 72, plunger stops 56 engage center plate 40 to prevent further travel of top plate 52.

Referring now to Figs. 11 and 12, operation of system 10 to aspirate and dispense liquids will be described. Initially, an 864 well plate 100 is placed onto tray 22. Motor 24 is then actuated to raise arm 22 until needles 72 are placed into the wells of plate 10. Preferably, sliding mount 30 is in the position shown in Fig. 12 where plunger stops 56 are in contact with center plate 40. Motor 36 is then actuated to raise sliding mount 30 along track system 34. In so doing, liquids within the wells of plate 10 are aspirated into needles 72. Motor 36 is controlled to control the amount of movement of mount 30. In this way, the volume of liquid aspirated into each needle may be precisely controlled.

Tray 22 is then lowered and plate 100 is removed and replaced with another plate 100 which is to receive liquids into its wells. Tray 22 is then raised until needles 72 are positioned within its wells as shown in Fig. 11. Mount 30 is then moved from the position shown in Fig. 11 back to the position shown in Fig. 12 to dispense the liquid from the needles. Tray 22 may then be lowered and plate 100 removed.

When dispensing liquids, it will be appreciated that the amount of movement of mount 30 may be controlled to control the amount of liquids dispensed. As such, mount 30 need not be moved until stops 56 engage center plate 40. It will also be appreciated that system 10 may be employed to dispense liquids into wells which are either empty or partially filled with another liquid. For instance, in some cases, it may be advantageous to dispense into partially filled wells since this increases the level of precision.

When dispensing liquid in volumes of less than about 1 µl into dry wells, it may be desirable to provide a hydrophobic coating on the needles as previously described. With such a configuration, tray 22 may be raised until the liquid droplets contact the bottom of the wells. When tray 22 is lowered, the liquid droplets adhere to the bottom of the wells, thereby transferring the liquid from the needles and into the wells.

System 10 is useful with a wide variety of liquids. For example, liquids such as DMSO, aqueous solvents, and the like may be utilized with system 10. Further, because the syringes are constructed of stainless steel and are generally inert to a wide variety of chemicals, system 10 may be used in connection with a variety of chemical processes.

EXAMPLE

A fluid dispensing system which is constructed essentially identical to system 10 of Fig. 1 was employed to dispense a liquid into the wells of an 864 well plate. The wells of the plate were pre-filled with about 10 µl of a buffer solution. The type of liquid aspirated into each of the needles was a fluorocine dye. Sliding mount 30 was lowered to dispense about 2 µl of the dye into each well. The maximum fluorescent count for any well was 218.77 and the minimum was 36.84. The average was 166.75. The standard deviation was 10.68 and the precision percentage was 6.40 percent CV.

The invention has now been described in detail for purposes of clarity of understanding. However, it will be appreciated that certain changes and modifications may be made. Hence, the invention is not limited by the foregoing but entitled to the full scope of protection outlined in the following claims as well as the full equivalents to which those claims are entitled.

WHAT IS CLAIMED IS:

1. A liquid dispenser, comprising:

a base member;

at least 864 syringes operably coupled to the base member, wherein each syringe has a distal tip, wherein the syringes are each configured to aspirate and dispense a substantially equal volume of liquid, and wherein the syringe tips are disposed within an area that is less than about 80 cm^2.

2. A liquid dispenser as in claim 1, wherein the syringe tips are spaced apart such that they are configured to be received into 864 wells of an 864 well plate.

3. A liquid dispenser as in claim 1, wherein each syringe is configured to aspirate and dispense liquid having a volume in the range from about 10 nl to about 10 µl.

4. A liquid dispenser as in claim 1, further comprising a hydrophobic coating disposed on a distal tip and an outside surface of each syringe.

5. A liquid dispenser as in claim 4, wherein the coating comprises a silicone based coating.

6. A liquid dispenser as in claim 1, further comprising an actuation assembly to actuate aspiration and dispensing of the liquid.

7. A liquid dispensing system comprising:

a base member;

a movable mount movably coupled to the base member;

a plurality of syringe units removably mounted to the mount, wherein each syringe unit includes an array of syringes, and wherein the syringes are configured to aspirate and dispense a liquid upon movement of the mount.

8. A system as in claim 7, further comprising a tray which is adapted to receive a multi-well plate, and wherein the tray is configured to move the multi-well plate such that the syringes are placed into the wells of the plate.

9. A system as in claim 7, wherein each syringe unit includes a 24 by 4 array of syringes, and wherein the moveable mount is configured to hold nine syringe units.

10. A system as in claim 7, wherein each syringe includes a syringe body and a plunger which is movable within the syringe body to aspirate liquids into the syringe body and to dispense liquids from the syringe body.

11. A system as in claim 10, wherein each plunger is operably coupled to the moveable mount such that movement of the moveable mount moves the plungers within the syringe bodies.

12. A system as in claim 11, wherein a proximal portion of each syringe body is collapsible when the mount is moved to move the plungers.

13. A system as in claim 12, wherein the proximal collapsible portion comprises a tubular outer guide which slides over a tubular inner guide.

14. A system as in claim 12, further comprising a fixed mount disposed to hold a distal portion of the syringe bodies.

15. A liquid dispenser as in claim 7, further comprising a hydrophobic coating disposed on a distal tip and an outside surface of each syringe.

16. A liquid dispenser as in claim 15, wherein the coating comprises a silicone based coating.

17. A syringe assembly comprising:

at least one tubular plunger guide;

a needle having a lumen which is aligned with the plunger guide and which terminates at an open distal tip;

a plunger moveable within the plunger guide and the needle; and

a sealing mechanism comprising a tubular seal member disposed between the plunger guide and the needle and a biasing system to force the plunger guide and the needle against the seal member such that a seal is formed between the needle and the plunger guide and between the plunger and the seal member such that liquids may be

aspirated into the lumen of the needle when the plunger is retracted, and liquids may be dispensed from the lumen of the needle when the plunger is extended.

18. An assembly as in claim 17, further comprising a pair of tubular plunger guides, wherein one of the guides is an inner guide and the other is an outer guide, wherein the inner guide is disposed within the outer guide, and wherein the plunger guides slide relative to each other during movement of the plunger.

19. An assembly as in claim 18, further comprising a guide plate disposed to maintain the inner and outer plunger guides in axial alignment.

20. An assembly as in claim 18, further comprising a center plate and a lower plate which are fixed relative to each other, wherein the needle is held by the lower plate, and the inner guide is held by the middle plate.

21. An assembly as in claim 20, further comprising a top plate, wherein both the outer guide and the plunger are coupled to the top plate, and wherein the top plate is moveable relative to the middle plate to move the plunger within the needle.

22. An assembly as in claim 21, further comprising a stop to limit the movement of the top plate relative to the center plate.

23. An assembly as in claim 20, wherein the biasing system comprises a protrusion coupled to the inner guide, and a biasing member disposed between the center plate and the protrusion to force the inner plunger guide against the seal member.

24. An assembly as in claim 17, wherein the needle has a distal portion with an outer diameter that is less than about 0.8 mm.

25. An assembly as in claim 17, wherein the needle is capable of dispensing liquids having a volume in the range from about 10 nl to about 10 μl.

26. An assembly as in claim 17, wherein the distal tip and an outside surface of the needle includes a hydrophobic coating.

27. A syringe assembly for dispensing volumes of liquid that are less than about 1 μl, comprising:

a needle having an outside surface and a lumen which terminates at an open distal tip;

a plunger moveable within the needle; and

a hydrophobic coating on the outside surface and the distal tip to permit a droplet to be formed at the distal tip when the plunger is moved within the lumen.

28. A syringe assembly unit comprising:

a plurality of syringe assemblies, with each syringe assembly comprising:

at least one tubular plunger guide;

a needle having a lumen which terminates at an open distal tip, wherein the needle is coupled to the plunger guide;

a plunger moveable within the plunger guide and the needle; and

a sealing mechanism disposed to form a seal between the needle and the plunger guide and between the plunger and the seal member such that liquids may be aspirated into the lumen of the needle when the plunger is retracted, and liquids may be dispensed from the lumen of the needle when the plunger is extended; and

a holding system to hold the syringe assemblies.

29. An assembly as in claim 28, wherein the holding system comprises a sliding mount and a fixed mount, and wherein the plungers are moved within the needles by movement of the sliding mount relative to the fixed mount.

30. An assembly as in claim 29, wherein the sliding mount is slidably coupled to a track, and further comprising a motor to move the movable mount along the track.

31. An assembly as in claim 28, wherein the holding assembly further includes a tray which is adapted to hold a multi-well plate.

32. An assembly as in claim 28, wherein the distal tip and an outside surface of the needle includes a hydrophobic coating.

33. A method for dispensing liquids, comprising:

providing a plate having at least 864 wells, wherein the wells are disposed within an area that is less than about 80 cm^2;

aspirating a liquid into at least 864 syringes;

dispensing a substantially equal volume of liquid from each syringe and into the well.

34. A method as in claim 33, further comprising aspirating and dispensing liquid having a volume in the range from about 10 nl to about 10 µl into and from each syringe.

35. A method as in claim 33, wherein each syringe has a syringe body and a plunger disposed within the syringe body, wherein the liquid is aspirated by retracting the plunger within a distal portion of the syringe body, and wherein the liquid is dispensed by extending the plunger within the distal portion.

36. A method as in claim 35, further comprising compressing a proximal portion of the syringe body to extend the plunger within the distal portion.

37. A method as in claim 33, further comprising initiating movement of each plunger at substantially the same time and moving each plunger at substantially the same rate.

38. A method as in claim 33, dispensing the liquid with a precision of less than about 6% CV at about 0.1 µl per well.

39. A method as in claim 33, further comprising incrementing the amount of liquid dispensed in increments in the range from about 10 nl to about 10 µl.

40. A method as in claim 33, further comprising preventing the liquid being dispensed from adhering to a distal tip or an outside surface of the syringe with a hydrophobic coating.

41. A method as in claim 40, wherein the volume of liquid is formed as a droplet having a volume that is less than about 1 µl during the dispensing step, and further comprising touching the droplet with a bottom end of the well to transfer the droplet from the syringe and into the well.

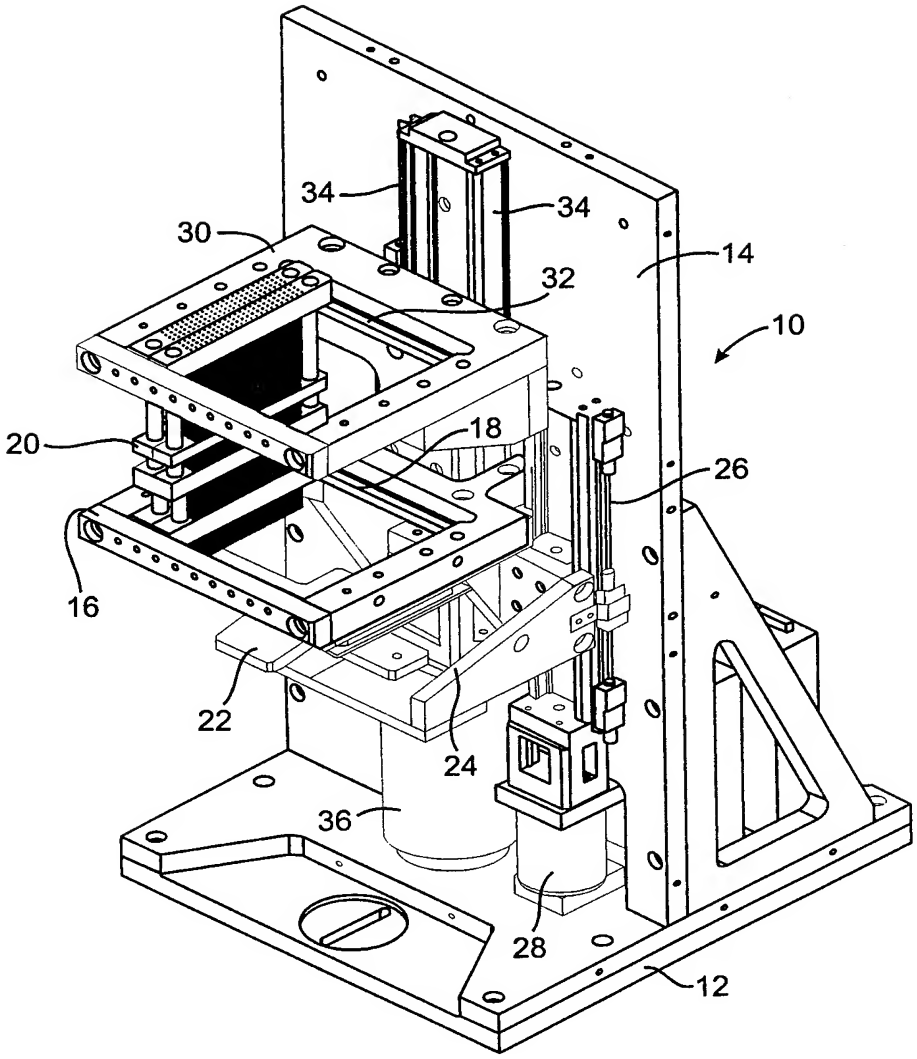


FIG. 1

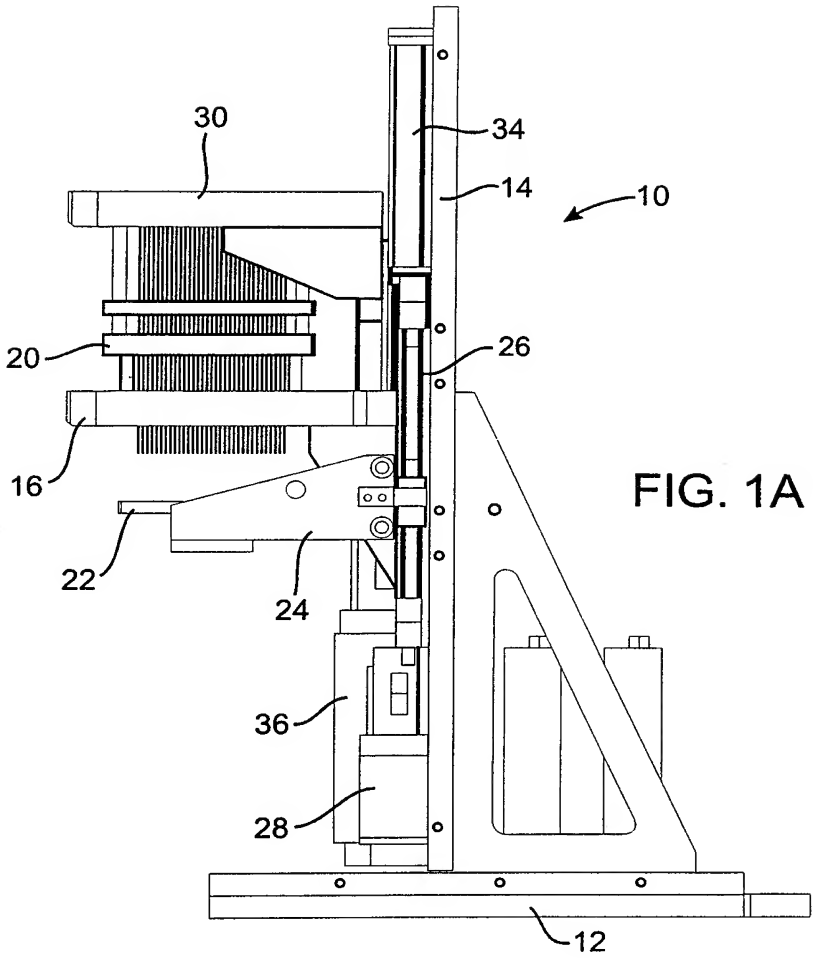


FIG. 1A

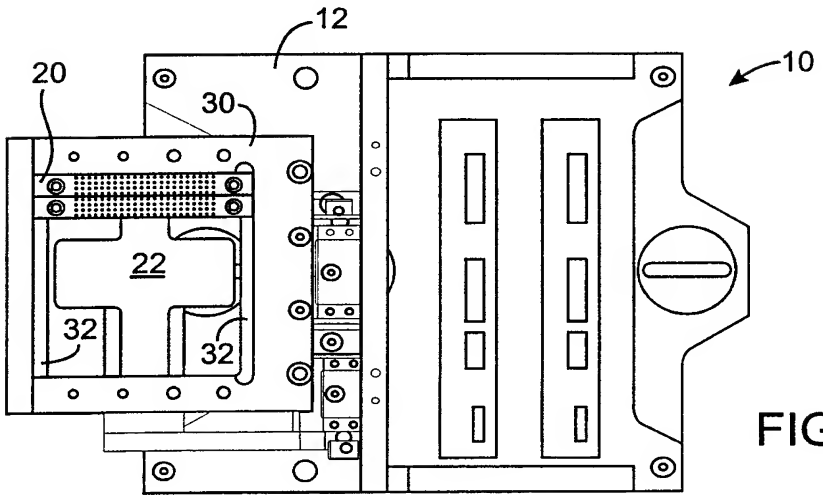


FIG. 1B

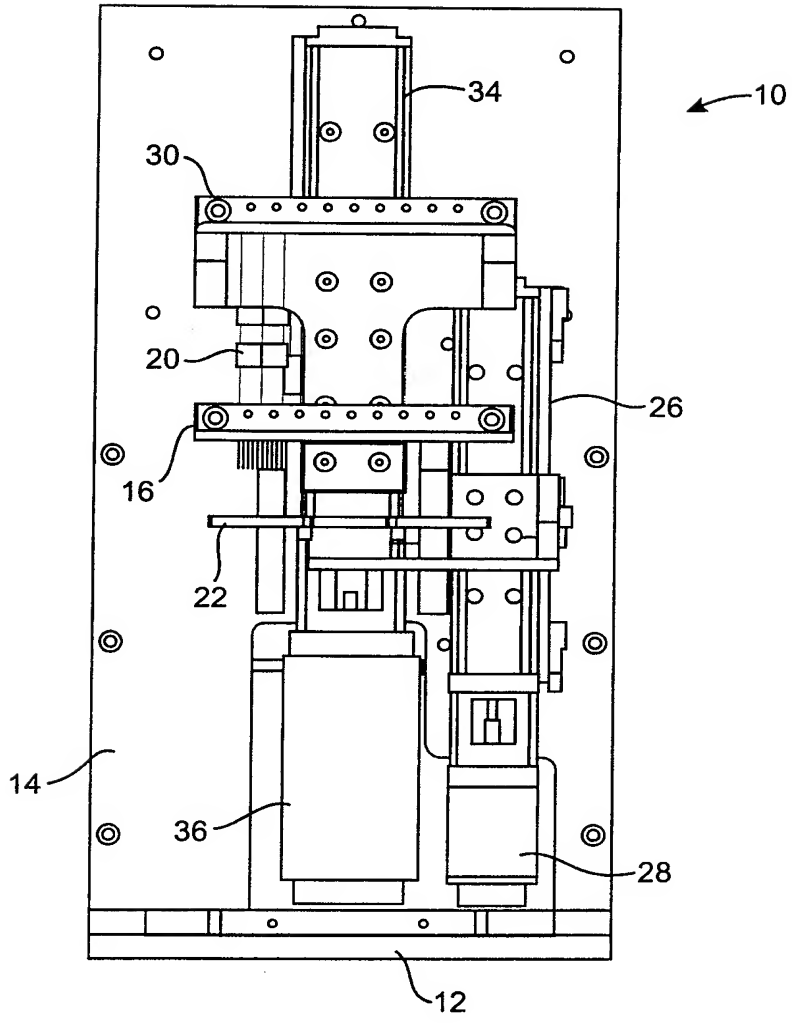


FIG. 1C

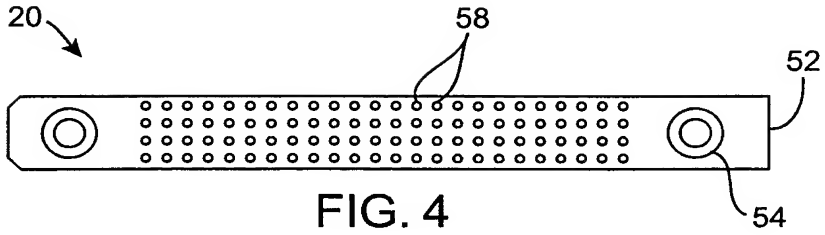


FIG. 4

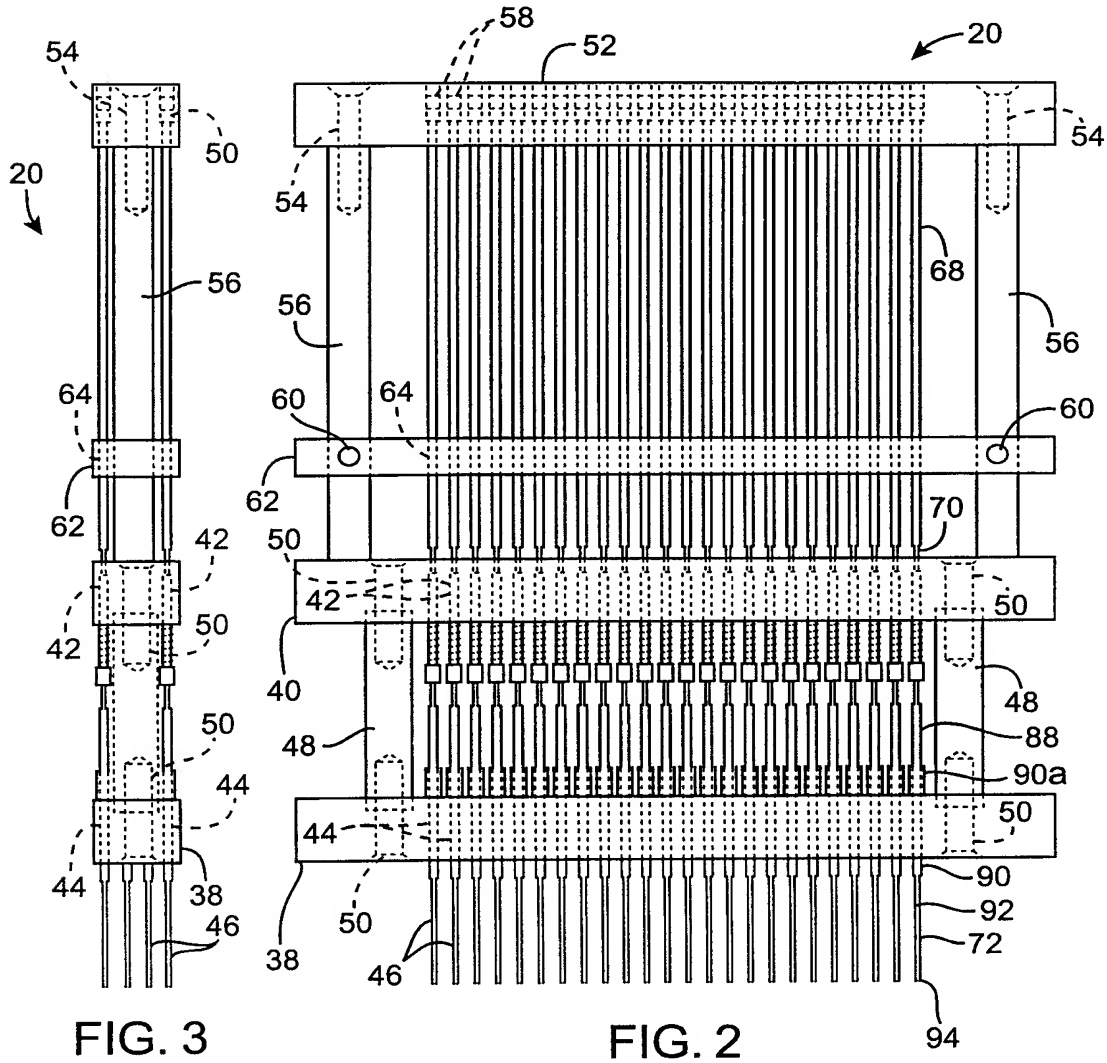


FIG. 3

FIG. 2

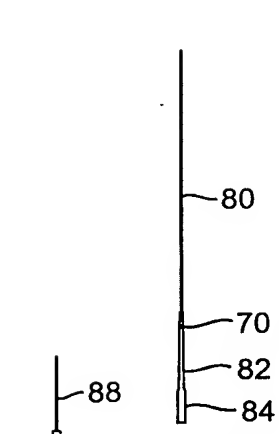


FIG. 7

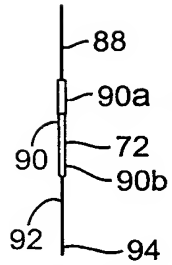


FIG.8

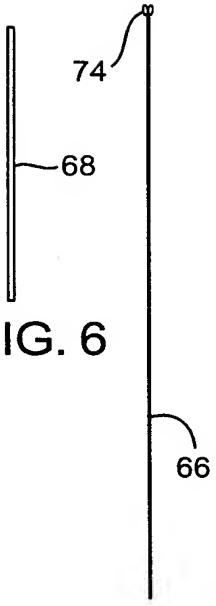


FIG. 6

FIG. 5

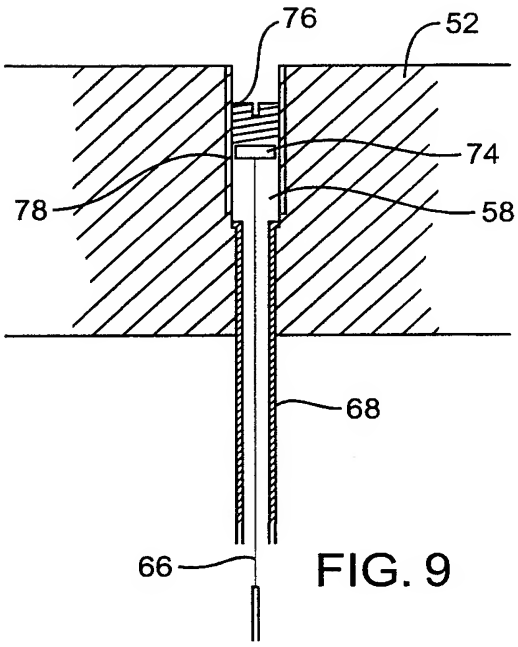


FIG. 9

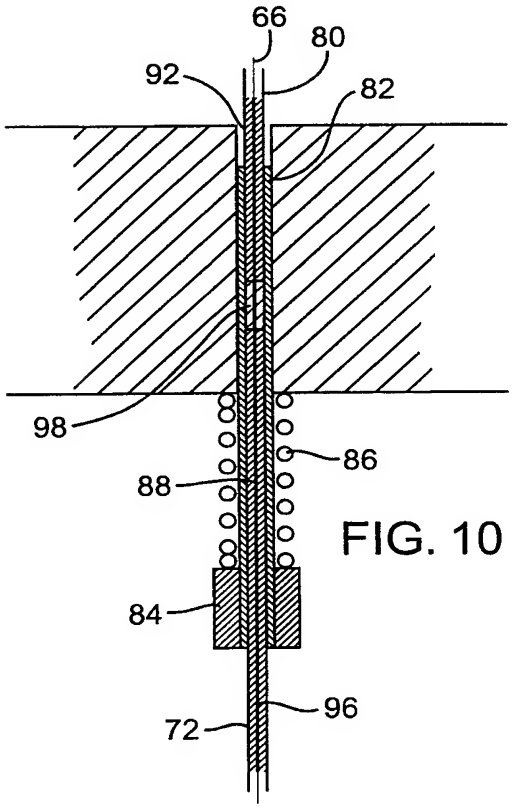
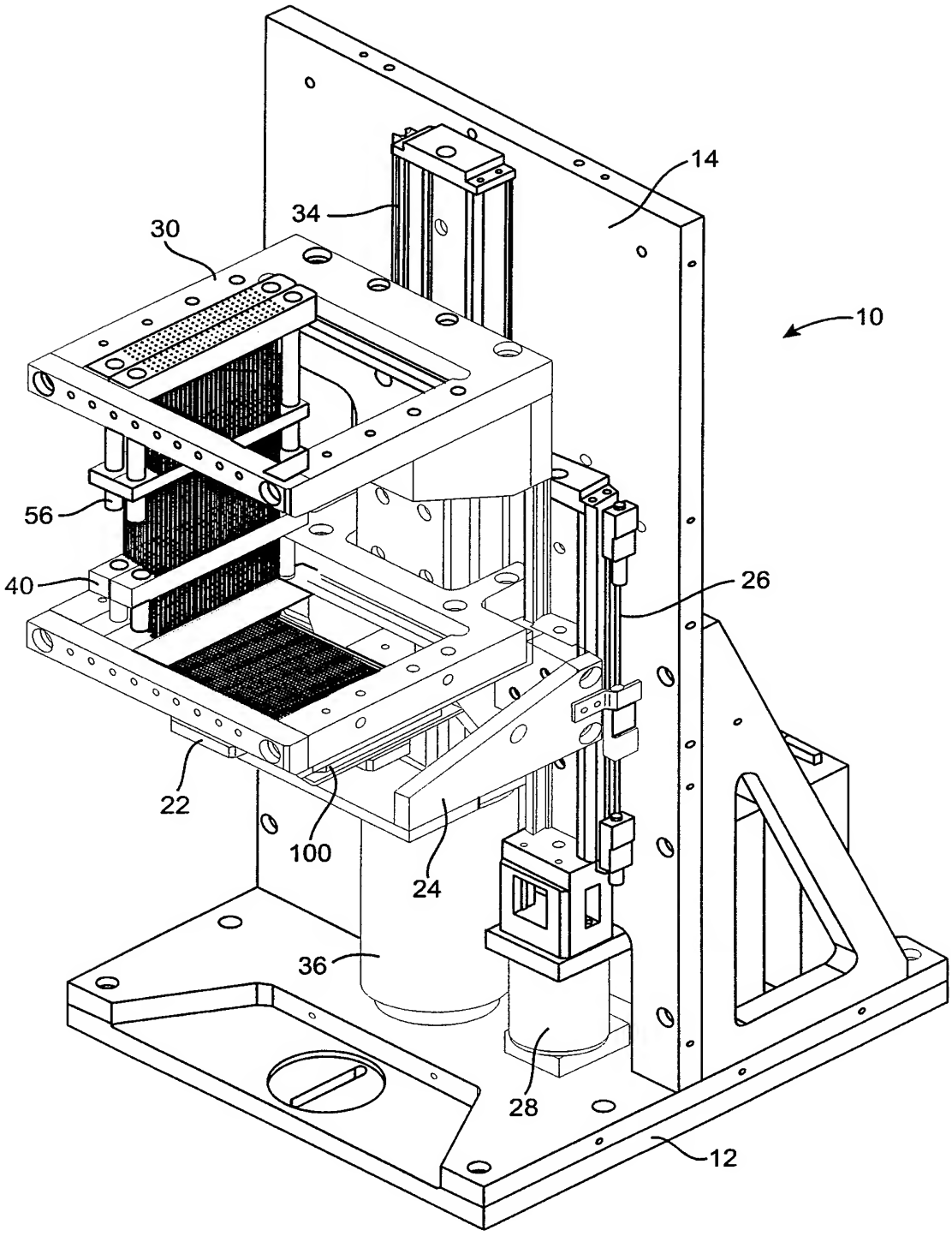


FIG. 10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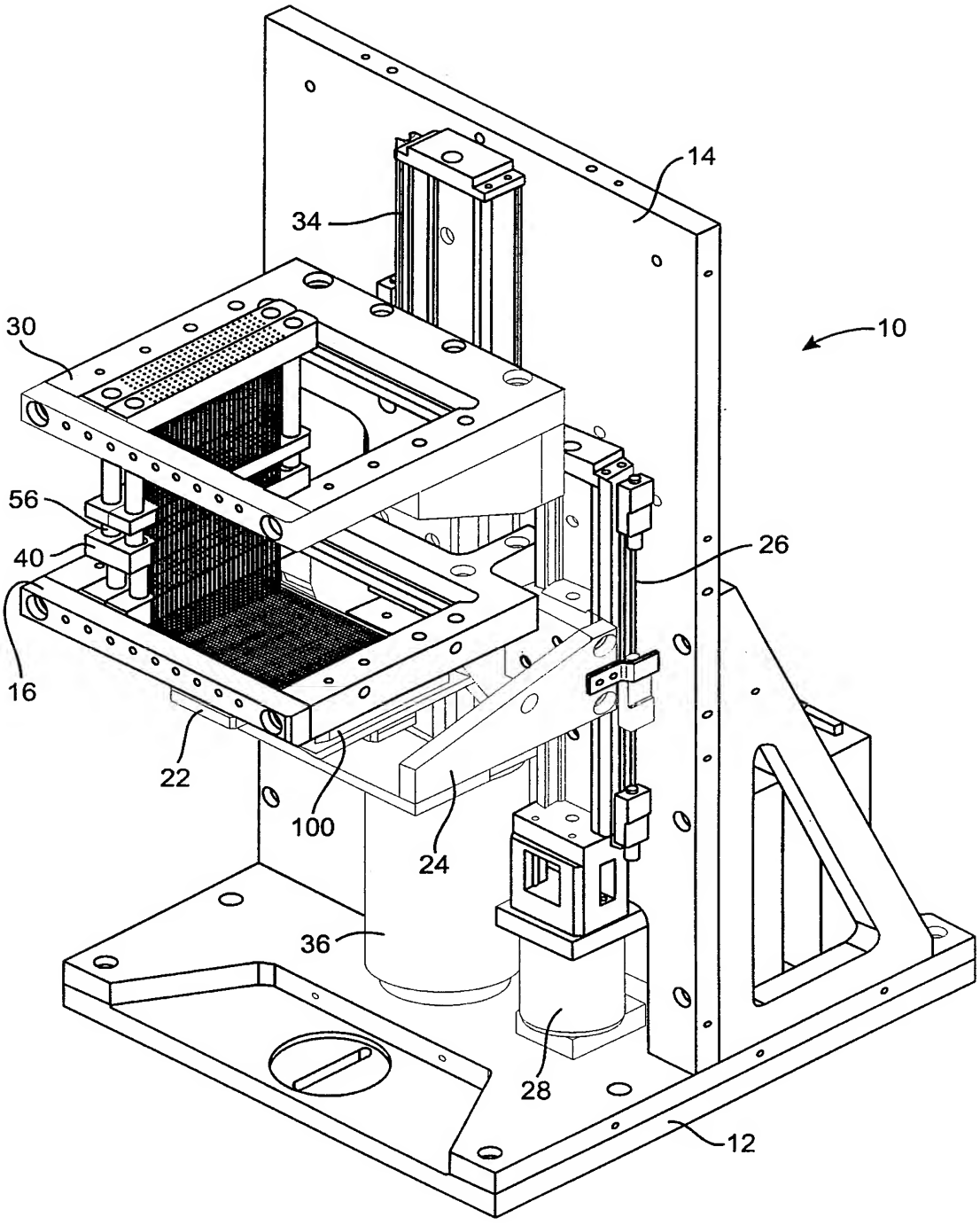
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04836

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :B01L 3/00, 3/02
US CL :73/863.32, 864.11, 864.13, 864.16, 864.17; 422/99, 100
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 73/863.31, 863.32, 864.11, 864.13, 864.16, 864.17; 422/99, 100, 104, 130, 131; 604/1-4, 207, 208

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST database
search terms: syringe array, pipet, needle, array, matrix, liquid dispen$4

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,621,665 A (WEBB) 11 November 1986, Figure 1.	1,2,4
Y	US 5,226,462 A (CARL) 13 July 1993, Figures 3 & 4, claims 13, 19.	1-4
Y	US 5,733,509 A (ACKLEY et al) 31 March 1998, column 3, line 10, col. 4, l. 35.	3, 39
Y	US 5,853,894 A (BROWN) 29 December 1998, column 5.	4, 40
A	US 5,849,598 A (WILSON et al) 15 December 1998, entire document.	
A	US 4,554,839 A (HEWETT et al) 26 November 1985, entire document.	

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	
"E" earlier document published on or after the international filing date	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"&" document member of the same patent family	

Date of the actual completion of the international search 19 MAY 2000	Date of mailing of the international search report 15 JUN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DWAYNE K. HANDY Telephone No. (703) 308-0661

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04836

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,555,957 A (FRANKEL et al) 03 December 1985, entire document.	
A	US 4,586,546 A (MEZEI et al) 06 May 1986, entire document.	
A	US 4,952,518 A (JOHNSON et al) 28 August 1990, entire document.	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04836

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6 and 33-41

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04836

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-6 and 33-41, drawn to a liquid dispenser and the method of using the dispenser.
Group II, claim(s) 7-16, drawn to a liquid dispensing system.
Group III, claim(s) 17-32, drawn to a syringe assembly unit.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: they lack a common special technical feature. Group I is drawn to a dispenser with a base member and a number of syringe tips disposed within a area. Group II contains a base, a movable mount and a plurality of syringe units. Group III is drawn to a syringe assembly.